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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,679	02/11/2002	Stephen Mayo	A-71138-1/RFT/RMS/RMK	9173

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EXAMINER	
BORIN, MICHAEL L	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/074,679	MAYO ET AL.	
	Examiner	Art Unit	
	Michael Borin	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *petition of 22 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Petition

1. Petition filed 09/22/2006 is acknowledged. Upon further consideration, the argument in petition is deemed persuasive and the Notice of non-responsive amendment is withdrawn. Consequently, the petition is moot.

Status of Claims

2. All previously pending claims are canceled. Claims 28-36 are added.

Applicants arguments have been considered but are deemed moot in view of the new claims in consideration and/or new grounds of rejection. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112, second paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 28-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 28, steps c), d): The claims are directed to the use of "high energy rotamers" (it is assumed that this refers to "high energy state rotamers – see step c)). The term "high energy state", based on the definition in the specification is vague and indefinite. The definition addressees "high energy state" as being anything in between high and low energy state:

"High energy state" is meant to include high energy states of the substrate on some reaction pathway, high energy states of the substrate/protein complex on some reaction pathway, transition states of the substrate on some reaction pathway, transition states of the substrate/protein complex on some reaction pathway, intermediate states of the substrate on some reaction pathway, intermediate states of the substrate/protein complex on some reaction pathway, low energy states of the substrate, low energy states of the substrate/protein complex, ground states of the substrate, and ground states of the substrate/protein complex.

As can be seen from the above list, "high energy state" rotamers can be, for example, either high- or intermediate- or low-energy states of substrate-protein complex (underlined above). Therefore, it is not clear what constitutes "high energy" state for such diversity of energy levels of rotamers.

B. Claim 28, step d): Although the step addresses protein design, the steps recited in the method step are directed to "analyzing", and it is not clear what constitutes "design" of a protein.

Claim Rejections - 35 USC § 102 and 103.

4. Claims 28,29,31 are rejected under 35 U.S.C.102(b) as anticipated by WO 9853849.

The instant claims are drawn to a method for screening for protozymes (or enzymes) , said method comprising:
a) identifying a suitable protein scaffold lacking a desirable enzyme-like activity;
b) inputting a protein backbone structure of said protein scaffold into a computer, wherein said backbone structure has variable residue positions ;
c) inserting an active site domain into said scaffold comprising use of one or more "high energy rotamers";
d) applying at least one protein design cycle; and
e) generating a set of candidate variant proteins with putative enzyme-like activity;
f) synthesizing plurality of candidate variant proteins, and
g) testing said candidate variant proteins.

WO 9853849 describes use of computer design method, DEZYMER, to introduce a catalytically active iron superoxide dismutase site into the hydrophobic core of Escherichia coli thioredoxin, a protein normally devoid of transition metal centers. The method can be used to redesign the hydrophobic interior of a protein (e.g., thioredoxin) and thereby introduce an iron center than can catalyze the dismutation of superoxide anion.

The following is recitation of the method steps of the reference (cited from paragraph bridging pages 25 and 26, and emphasized by italicizing) , which are compared to corresponding steps of the claimed method.

The rational design approach used in the referenced method is based on the placement of an active site into the framework of a known protein fold.

This step reads on the claimed step of inserting an active site into scaffold, wherein the scaffold is a parent protein lacking desired enzymatic activity. With regard to the limitation introduced into the base claim 28 of "comprising using high energy rotamers", the instant specification provides the following definition of "high energy state ":

"High energy state" is meant to include high energy states of the substrate on some reaction pathway, high energy states of the substrate/protein complex on some reaction pathway, transition states of the substrate on some reaction pathway, transition states of the substrate/protein complex on some reaction pathway, intermediate states of the substrate on some reaction pathway, intermediate states of the substrate/protein complex on some reaction pathway, low energy states of the substrate, low energy states of the substrate/protein complex, ground states of the substrate, and ground states of the substrate/protein complex.

As can be seen from the above list, "high energy state" rotamers will include any rotamers, as they can be, for example, either high- or intermediate- or low-energy states of substrate-protein complex (underlined above). Therefore, the active site introduced per referenced method is considered to comprise what is addressed in the instant claims as "high energy rotamers".

Further, in the referenced method,

DEZYMER algorithm systematically examines a protein structure to identify backbone positions that are arranged in such a way that appropriate rotamers the residues in the binding site definition can be placed to satisfy the desired ligand geometry. In the second phase, additional changes may be introduced to ensure steric complementarity of the placed site with the surrounding protein matrix. The intent being to maintain the original fold and stability of the host protein.

This step reads on the claimed step of "applying of at least one computational algorithm". With regard to recitation of steps of analyzing interaction with either "variable position rotamers" or with the "remainder of protein backbone", first, as all the claimed requires is application of "at least one" computational algorithm, at least interaction with some of the rotamers is being performed in the referenced method. Second, "ensuring steric complementarity with the surrounding protein matrix" in the referenced method is understood by Examiner as analyzing interaction of the inserted active side rotamers first with some selected "variable position rotamers" and then, with the "remainder" of protein backbone.

The candidate variant proteins are further synthesized and tested for the desired activity (see claim 1, for example).

With regard to claim 32, the referenced method creates "true active site which catalyzes the inner sphere transfer of electrons both to and from small molecule substrates" (p. 3, top) and introduces, for example, an iron center than can catalyze the dismutation of superoxide anion.

5. Claims 30, 32-36 are rejected under 35 U.S.C.103(a) as obvious over WO 9853849 in view of Dahiyat et al (IDS, referenceC13) or admitted prior art.

WO 9853849 is used as addressed above. The reference does not teach use of another particular protein design algorithm, such as DEE or force field. The objective of the method, however, is to ensure steric complementarity of the placed site with the surrounding protein matrix and to maintain the original fold and stability of the host protein. Therefore, it would be obvious to use any suitable method of protein design which would complement the design method described in WO 9853849 and ensure optimal spatial configuration of the designed modified protein. Dahiyat et al, for example[1], describes such method of protein design automation which uses discrete search algorithm based on DEE calculations and using Monte Carlo search and identification of high-scoring sequences (see Abstract). Although WO 9853849 does not teach all variations of the steps of the protein design, because the techniques of computational protein design are well known in the art (as described in Dahiyat et al, or also see references cited on p. 2, lines 35 to p.3, line 2), and because the selection of appropriate protein design steps is conventional and within the skill in the art to which

[1] The reference replaces US Patents 6,188,965, US 6,269,312, of the same research group, used in the previous Office action; Examiner agrees with applicant that these patents can be used only as 102(e) art, and therefore, removes the references from rejection under 103(a).

this invention pertains, it would be conventional and within the skill of the art to select appropriate protein design steps .

Conclusion.

6. No claims are allowed

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. The examiner can normally be reached on 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Borin, Ph.D.
Primary Examiner